

Introductory Remarks

Claims 3 and 4-15-in part are currently pending.

REMARKS

Claim Rejections-35 U.S.C. § 102

The Examiner rejected claims 3-15 under 35 U.S.C. § 102(a) as being anticipated by Kauvar et al. (WO 98/32017, 23 July 1998; PTO-1449).

Applicants respectfully traverse this rejection. Applicants respectfully submit that the Kauvar does not disclose the fitted quaternary structure of insulin receptor. It also does not disclose use of a processor, as recited in amended claim 3, to compare a compound to the fitted quaternary structure of insulin receptor and determine whether the compound modulates insulin receptor. Kauvar et al. primarily discloses binding assays to detect conformational change in IR caused by compounds binding to insulin receptor. The Kauvar patent application relies totally on the x-ray structure by Hubbard of the tyrosine kinase (TK) domain, only one of the many domains of IR. It invokes no quaternary structural relationship of this domain to any other intracellular or extracellular IR domain, nor of one tyrosine kinase to its partner in the IR dimer structure, which TK it must transphosphorylate for activation. The theoretical emphasis is on using the surface structure of the individual TK domain, with a focus on a "belt" region between the two subdomains of the TK itself. In practice the patent proposes the examination of different modifications of a specific class of chemical compounds.

In addition, there is no relationship between Kauvar et al and the present patent application. The Applicants' starting structure is the relative structural relationship of the atomic domains within the entire insulin receptor fitted to the compact quaternary structure. It is based on the fitted binding of insulin in the binding site with specific named amino acid side-chain interactions. It is further based on the mechanics of the function of insulin receptor as deduced from the quaternary structure, which requires the specific juxtaposition (quaternary structure) and

interaction of relevant domains. None of these interactions or juxtapositions are disclosed in any previous publications.

Therefore, since Kauvar et al. does not disclose all the elements of the amended claims, it cannot anticipate the amended claims. For the reasons given above, the claims would also not be obvious in view of Kauvar et al. Applicants respectfully request this rejection be withdrawn.

Claim Rejections-35 U.S.C. § 103

Claims 3-15 were rejected under 35 U.S.C. § 103(a) as being unpatentable under Lauri et al. in view of Christiansen et al.

Applicants respectfully traverse this rejection. To establish obviousness, the Examiner must make out a *prima facie* case that satisfies three requirements: 1) the references must teach or suggest all the claim limitations; 2) the prior art combined with general knowledge must include a suggestion or incentive to modify or combine the references and 3) the modification or combination must have a reasonable chance of success.

The Examiner acknowledged that the quaternary structure of insulin in the application has not been previously elucidated. The Applicants disagree with the Examiner's assertion that the instant invention is directed to nonfunctional descriptive material in that the structure which is fed into the computer algorithm is simply a set of data utilized for comparisons using a series of processing steps, and does not impose a change in the processing steps. The Examiner further asserted that the method to compare data does not become non-obvious merely because new data are available. The Examiner cited *In re Gulack*, 03 F.2d 1381, 1385 (Fed. Cir. 1983) in support of these statements.

The Applicants note that *In re Gulack*, the patent was allowed. The present application provides an even stronger case for patentability. *In re Gulack* involved a band with digits imprinted on the band and an algorithm to develop the digits. Uses of the band included educating about number theory.

After reviewing that case, the present invention cannot be characterized in any way as simply a rearrangement of nonfunctional descriptive material. *In re Gulack* shows that support of digits, display of digits and sequences of digits residing in a unique position with respect to each other are examples of a *functional* relationship involving descriptive material¹. The fitted quaternary structure of IR provides a structure where each atom is shown to be residing in a unique position with respect to every other atom. When the fitted quaternary structure is used on a processor (e.g., in a computer-implemented method), the processor also provides support and display for the fitted quaternary structure. There is a clear functional relationship between the

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Sections III and IV of *In re Gulack* include the following statements:

"The appealed claims, on the other hand, require a particular sequence of digits to be displayed on the outside surface of a band. These digits are related to the band in two ways: (1) the band supports the digits; and (2) there is an endless sequence of digits — each digit residing in a unique position with respect to every other digit in an endless loop. Thus, the digits exploit the endless nature of the band.

The differences between the appealed claims and Wittcoff reside in appellant's particular sequence of digits, and in the derivation of that sequence of digits. These features are critical to the invention disclosed by the appealed claims. Wittcoff neither discloses nor suggests either feature.

IV.

We reject the board's conclusion that there is no functional relationship between the printed matter and the substrate of the appealed claims. Such a relationship does exist and it is different from the relationship exhibited by the corresponding elements of the Wittcoff reference. We find no suggestion in the cited reference of appellant's particular sequence of digits Q or of the derivation of that sequence.

Reversed."

fitted quaternary structure of IR and a processor. Furthermore, dependent claims clearly include structure and functional elements by reference to elements such as *in vitro* and *in vivo* assays.

Furthermore, one would not arrive at the claimed invention when combining Laurie et al. with Christiansen et al. Christiansen et al. discloses a "gross quaternary structure" of human placental insulin receptor (see paragraph. 2, page 249) and does not provide an enabling disclosure of the insulin receptor quaternary structure or its conformational changes. The Christiansen et al. structure has poor resolution and is not useful for identifying modulators of IR activity. The article states that, "After insulin-stimulated phosphorylation of the solubilized receptor, we have not within the limits of resolution in the electron microscope been able to detect alterations in the T-shaped structure." In contrast, the conformational changes are disclosed in great detail in the present patent application. Thus, the cited reference neither discloses nor suggests the fitted quaternary structure of insulin receptor or its conformational changes upon ligand binding. It also does not disclose use of a processor to compare a compound to the fitted quaternary structure of insulin receptor and determining whether the compound modulates insulin receptor. The differences between the claimed invention and the prior art are sufficient to establish inventiveness of the claims over the cited art.

The Christiansen et al. quaternary structure based on negatively stained specimens has never resulted in insights into the structure, in terms of insulin binding, nor in terms of the function of the receptor. The elongated, T- or Y-shaped structure observed by Christiansen is quite different from the compact structure in the present application. That elongated structure is now recognized as not being the native structure; e.g., De Meyts and Whittaker, *Nature Review* 1 (Oct.), 769-783, 2002, published after the Applicants' filing date, say that in showing such an elongated form as a linear arrangement of domains in their review, they "do not imply that the

actual structure of the receptor has such a stretched-out configuration, which is not supported by recent electron microscopic studies", and that it is likely that IR "is a globular molecule that has a diameter of 150 A [Angstrom]." The latter is the Applicants' structure. In retrospect it is likely that the negative stain in the work of Christiansen et al has resulted in a partially denatured structure that gives the elongated appearance.

The elongated structure does not place the individual domains in the correct quaternary arrangement on the IR monomer, e.g., in the elongated structure the Fn2 domain is well separated from the Cys-rich domain, whereas in the Applicants' structure Fn2 is near the Cys-rich domain, with consequences for IR function. Similarly, the two covalently linked IR monomers that make up the dimer would also be incorrectly positioned with respect to each other and not permit a joint binding of a single insulin molecule. Thus, even with today's knowledge of the atomic structure of some of the individual subdomains of IR, such as the tyrosine kinase, and analogous structures such as the IGF-1R L1-Cys-rich-L2 domains, the fitting of such domains using programs like CAVEAT, published by Lori and Bartlett (1994), will not, even today, produce a correct atomic model for the total IR.

In contrast, the conformational changes are disclosed in great detail in the present patent application. Thus, the cited art neither discloses nor suggests the fitted quaternary structure of insulin receptor or its conformational changes upon ligand binding. It also does not disclose use of a processor to compare a compound to the fitted quaternary structure of insulin receptor and determining whether the compound modulates insulin receptor. The differences between the claimed invention and the prior art are sufficient to establish inventiveness of the claims over the cited reference.

CONCLUSION

Applicants submit that in light of the foregoing amendments and remarks the claims are in a condition for allowance. Reconsideration is respectfully requested.

Please charge Deposit Account No. 26-0084 \$ 465.00 (small entity fee) to cover the cost of a 3-month Extension Fee.

No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Respectfully submitted,



EDMUND J. SEASE, Reg. No. 24,741
McKEE, VOORHEES & SEASE, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No: (515) 288-3667
Fax No: (515) 288-1338
CUSTOMER NO: 22885

Attorneys of Record

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